On page 2, line 3, please replace "manu" with --many--.

On page 9, line 11, please replace "fromn" with --from--.

On page 11, line 28, please replace "expresing" with --expressing--.

On page 25, line 24, please replace "polyuethyleneimine" with --polyethyleneimine--.

IN THE CLAIMS

5. (Amended) A reagent according to Claim 1 wherein the specific binding compound is a [a] specific binding peptide comprising 4 to 100 amino acids.

REMARKS

1. Status of the Claims

Claims 1-4, Claim 5, as amended, and Claims 6, 9, 10 and 18-21 are pending in the application. Claims 7, 8, 11-17 and 22-23 are withdrawn from consideration by the Examiner pursuant to the restriction requirement mailed February 22, 1996 and Applicants' election with traverse. Applicants respectfully request that Examiner Davenport reconsider their traversal of the restriction requirement, which is now deemed final. Upon allowance of the pending claims, Applicants will cancel the withdrawn claims if the Examiner decides to maintain the restriction after reconsideration.

Applicants also acknowledge withdrawal of the previously-made rejection of the pending claims with regard to the scope and nature of the substituent "Z" in the radiolabel binding moieties of the invention.

2. The Claims, as amended, fulfill the requirements of 35 U.S.C. §112.

Claims 1-6, 9, 10 and 19-21 stand rejected on 35 U.S.C. §112, first paragraph grounds for the reasons asserted in the previous Official Action. Applicants respectfully request reconsideration of this rejection in view of the following argument.

The asserted basis for this rejection is that under experimentation would be involved for one of ordinary skill in the art to obtain a "specific binding compound" to produce a reagent of

the invention. The asserted unpredictability in the art with regard to *in vivo* localization is asserted, again using the *Fischer* case as precedent. Applicants appreciate the Examiner's position with regard to the teachings of *Fischer*, but continue to insist that *on the facts* the case is a horse of a different color from the instantly-claimed invention, for all of the reasons proffered in their last response, which were deemed unpersuasive. Even without reference to the *Fischer* case, however, Applicants understand that the gist of the Examiner's objection is that the specification does not support the fullest scope of the claims.

Applicants respectfully request that this objection be considered in view of two types of "evidence" on the extent of support found in the specification and in the extent of the burden imposed on the worker of ordinary skill in making the claimed invention using the specification and what is known in the art. First, Applicants respectfully request that the explicit teachings of their specification be considered:

> For purposes of this invention, the term "specific binding compound" is intended to mean any compound that specifically binds to a target site in a mammalian body. "Specific binding" will be understood by those with skill in this art as meaning that the compound localizes to a greater extent at the target site that to surrounding tissues. Such specific binding is advantageous because scintigraphic imaging agents comprising such specific binding compounds are distributed within a mammalian body after administration to provide visual definition of the target *in vivo*. Specific binding compounds include but are not limited to peptide, oligosaccharides, nucleotides, oligonucleotides and polynucleotides, and specific receptor-binding compounds.
>
> Each specific-binding peptide-containing embodiment of the invention is comprised of a sequence of amino acids. The term amino acid as used in this invention is intended to include all L- and D-, primary α- and β-amino acids, naturally occurring, modified, substituted, altered and otherwise. Specific binding peptide embodiments of the reagents of the invention comprise specific binding peptides having a molecular weight of about 5,000 daltons. Particularly preferred embodiments of the specific binding peptides of the invention include peptides that bind with high affinity to the platelet GPIIb/IIIa receptor. In additional preferred embodiments, the specific binding peptides include peptides that bind specifically to the somatostatin receptor (SSTR) on SSTR-expressing cells, particularly tumor cells and activated T-lymphocyte cells. Reagents comprising specific-binding peptides provided by the invention include but are not limited to reagents comprising peptides having the following amino acid sequences (the amino acids in the following peptides are L-amino acids except where otherwise indicated):

cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGC.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCK.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCR.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCRD.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCRK.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCRR.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCKK.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCKKK.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGC.Orn.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCKDK.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGC.Orn.D.Orn.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGC.Orn.D.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.KKC.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.KRC.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.RRC.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.KKCK.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GRCK.amide)
cyclo(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GKCR.amide)
CH_2CO.Y$_D$.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGC.amide
CH_2CO.Y$_D$.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGCG.amide
CH_2CO.Y$_D$.Apc.GDCGGSSGGCG.amide
CH_2CO.Y$_D$.Apc.GDCGGCG.amide
GRGDGGC
GLFCGC.amide
GRGDGGGGC
F$_D$FYW$_D$KTFTGGC.amide
acetyl.CGGY.[$(CH_2)_4$-piperidine]

(Single-letter abbreviations for amino acids can be found in G. Zubay, *Biochemistry* (2d. ed.), 1988 (MacMillen Publishing: New York) p.33; other abbreviations are as in the Legend to Table I). This list of reagents provided by the invention is illustrative and not intended to be limiting or exclusive, and it will be understood by those with skill in the art that reagents comprising combinations of the peptides disclosed herein or their equivalents may be covalently linked to any of the chelating moieties of the invention and be within its scope, including combinations of such peptides and chelating moieties comprising linking groups as disclosed herein.

For optimal imaging using one embodiment of the invention, the reagent must be capable of binding to the platelet GPIIb/IIIa receptor with sufficient affinity that it inhibits the adenosine diphosphate (ADP)-induced aggregation of human platelets in a standard platelet aggregation assay (*see* Example 3 *below*) when present at a concentration of no more than 0.3 μM.

In certain embodiments of the reagents of the invention, β-glucans comprise the specific binding compound component. For the purposes of this invention, the term "β-glucan" is intended to mean oligosaccharides comprising 1,3- and 1,6-linked β-D-glucose residues wherein the β-glucan moiety has a molecular weight of up to about 2,000 kilodaltons. One preferred embodiment of β-glucan-containing reagents of the invention has formula:

β-glucan-(=NNHCO.$(CH_2)_3$CO.)GGC.amide

(p.11, line 11 through p.13, line 11). In addition, Applicants' specification explicitly teaches determination of platelet aggregation inhibition *in vitro* using an assay appreciated in the art as being predictive of localization at sites of infection and inflammation *in vivo* (Example 3); atherosclerotic plaque localization in rabbits *in vivo* (Example 5); and specific binding of radiolabeled peptides at sites expressing somatostatin receptors (SSTR), both *in vitro* and *in vivo* (Example 7), as well as teaching *in vivo* deep vein thrombosis imaging methods (Example 4) and *in vivo* infection imaging (Example 6). Applicants respectfully submit that these teachings explicitly define the scope and meaning of the terms used in the claims, and providing the skilled worker with sufficient guidance to know what it is that the inventors claim as their own.

Second, the question raised by the Examiner is whether, once the worker knows what the invention is, can he or she produce a reagent of the invention without undue experimentation. Applicants request reconsideration of the evidence submitted as part of the database search previously filed in support of their earlier response. Applicants respectfully reiterate their contention that the discovery of specific binding compounds (peptides and otherwise) ***is not*** what they have claimed. Applicants claim such specific binding compounds radiolabeled using the means and methods disclosed in their specification: by covalently linking a radiolabel binding moiety as defined in their specification that can be radiolabeled most preferably with Tc-99m. This *combination* of a specific binding peptide, whatever its source, and the radiolabel binding moieties of the invention provide the skilled worker with the means to radiolabel ***any*** particular specific binding peptide. Applicants have provided illustrative examples throughout their specification of how to make such specific binding compounds (Example 1), how to radiolabel the compounds (Example 2), and how to characterize the *in vivo* capacity of such radiolabeled compounds to provide a useful scintigraphic image of a particular site (Examples 3 through 7).

Applicants respectfully contend that this is all they are required to do, regardless of the amount of experimentation required, since the experimentation is clearly routine: determine a specific binding compound from the scientific literature, prepare a reagent comprising the specific binding compound covalently linked to a radiolabel binding moiety of the invention, radiolabel with reagent, and determine whether it is capable of providing the required scintigraphic image using any of the test experimental systems disclosed in the specification. Applicants submit that the mere fact that *each and every embodiment* of the reagents of the invention may not be optimally useful for scintigraphic imaging does not preclude the patentability of the pending claims, since the patent law does not require such a draconian measure of enablement. Applicants respectfully contend that the skilled worker could practice the claimed invention, using the teachings of the specification and the skill in the art, to select a specific binding compound for any particular site to be imaged, to make a radiolabeled embodiment of a reagent of the invention comprising said specific binding compound, and to determine whether or not a scintigraphic image sufficient to be useful results. Having satisfied this level of enablement, Applicants respectfully contend that the lack of absolute certainty in using any particular specific binding compound does not violate the rubrics of 35 U.S.C. §112, first paragraph.

Applicants respectfully request reconsideration of the pending claims in view of their argument herein, and respectfully submit that this argument has traversed the stated ground of rejection. Withdrawal of rejection on 35 U.S.C. §112, first paragraph grounds is therefore respectfully solicited.

CONCLUSIONS

Applicants believe that rejections under 35 U.S.C. §112 have been overcome by amendment or traversed by argument, and that all requirements for patentability have been met. They respectfully request that these Claims be brought to issue.

If Examiner Davenport believes it to be helpful, she is invited to contact the undersigned attorney by telephone at (312) 913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Date: June 23, 1997

By: _____
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